Endogenous angiotensin II and baroreceptor dysfunction: a comparative study of losartan and enalapril in man

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Aims To assess the role of direct AT1 receptor antagonism in baroreceptor modulation in man, and to perform a direct comparison of Ang II blockade at the receptor level with that of ACE inhibition.

Methods Ten healthy male volunteers [mean age (s.d.) 23 (6.9)] pretreated with frusemide therapy (40 mg day^{-1} for 3 days prior to each visit) were studied on 3 separate days, 10 days apart, in a placebo-controlled, randomized, double-blind, cross-over fashion. On each study day, subjects were randomly given either a single-dose of enalapril 20 mg, losartan 50 mg or placebo. Baroreceptor function was assessed by measuring changes in blood pressure (BP), pulse interval (RR Int) and heart rate (HR) in response to incremental doses of intravenous phenylephrine infusions (0.2–3.6 $\mu g\ kg^{-1}\ min^{-1}$).

Results In response to phenylephrine, no significant differences in BP responses were observed with any of the study medications but reflex heart rate responses were significantly increased with both enalapril and losartan compared with placebo ($P<0.05$). The (RR/ΔsBP ratio, taken as a measure of baroreceptor sensitivity (BRS) was significantly increased with enalapril [12.2 + 4.6 ms $mmHg^{-1}$ (mean + s.d.)] and losartan [11.9 + 3.6 ms $mmHg^{-1}$] compared with placebo [9.2 + 4.5 ms $mmHg^{-1}$]; i.e. enalapril and losartan increased the (RR/(ΔsBP ratio by 3.0 ms $mmHg^{-1}$ (95%CI 0.5, 5.6; $P<0.05$) and 2.8 ms $mmHg^{-1}$ (95%CI 0.6, 5.0; $P<0.038$), respectively. There were however, no significant differences between losartan and enalapril [mean difference 0.25 (95%CI −1.6, 2.1)].

Conclusions The present study confirms observations from animal models that blocking *endogenous* angiotensin II in man improves baroreceptor function. Both strategies, AT1 receptor antagonism and ACE inhibition appear to be equally effective in restoring baroreceptor function in salt-depleted normotensive subjects.

Keywords: angiotensin II, baroreceptor, enalapril, losartan

Introduction

Baroreflex dysfunction is thought to be a key process leading to ventricular dysrhythmias and sudden deaths in patients with CHF and in postmyocardial infarction patients [1–3]. A major component of baroreflex dysfunction is vagal activity. In animal studies [4, 5], vagal stimulation dramatically improves survival and reduces dysrhythmias after coronary artery ligation.

It is well established that angiotensin II (Ang II) attenuates baroreflex control of heart rate and increases sympathetic activity [6, 7]. Similarly, ACE inhibitors have been shown to improve both heart rate variability and baroreceptor sensitivity (BRS) in man [8–10]. Indeed, the effect of ACE inhibitors on BRS may well be instrumental in their ability to improve mortality in heart failure.

Compared with ACE inhibitors, Ang II type 1 receptor (AT1) antagonists offer a more selective and complete blockade of Ang II. The question naturally arises whether AT1 receptor antagonists will also have favourable effects on BRS. Pharmacologically, they may even be more effective at boosting BRS because Ang II levels are not completely suppressed by ACE inhibitors [11]. However, although direct AT1 receptor antagonists have been shown to improve baroreceptor function in animal models [12, 13], the only study to examine this question in man found no effect of losartan on baroreflex sensitivity [14]. This whole question has been given added impetus by the recent Evaluation with Losartan in the Elderly (ELITE) trial results. Although designed primarily to assess safety and efficacy of the treatments and not mortality, it was intriguingly observed in the multicentre ELITE trial [15] that those randomized to losartan had a 46% reduction in all-cause mortality in comparison with captopril-treated patients, which was primarily due to a decrease in sudden cardiac deaths.

The purpose of the present study was two fold. Firstly, the main aim was to assess if AT1 receptor antagonism really does improve baroreceptor function in man, as had been previously demonstrated in animal models although it did not appear to in the only human study of the matter [14]. The secondary aim was to perform a head to head

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comparison of Ang II blockade at the receptor level with that of ACE inhibition to see if there were any major differences between them which might be relevant to the ELITE results. In this study, a comparison of a single oral dose of losartan potassium 50 mg was made with a single dose of an ACE inhibitor, enalapril maleate 20 mg. In particular, we performed this study in normal man in whom the endogenous renin angiotensin system (RAAS) had been activated as it would enable us to assess the activated RAAS of heart failure in isolation while avoiding the confounding influences of increased age, comorbidity and polypharmacy which would be present in CHF.

Methods

Subjects

Ten normal male volunteers [mean age (s.d.) 23 (6.9)] were studied. None had a history of hypertension or cardiac disease. Physical examination, routine haematological and biochemical parameters, and 12 lead electrocardiograms (ECG) were normal in all subjects. Each provided informed consent in writing, and the study was approved by the Tayside Ethics Committee on Medical Research.

Protocol

Subjects were studied on 3 separate days, 10 days apart, in a placebo-controlled, randomized, double-blind, cross-over fashion. Three days prior to each study visit, subjects were pretreated with oral frusemide 40 mg day^{-1} to activate their endogenous renin-angiotensin system. The subjects were instructed to take the daily frusemide dose at 18.00 h and they were asked to maintain their usual diet for the duration of the study and to adhere to the same pattern of meals in the 48 h preceding each visit day. Subjects were also required to refrain from alcohol, caffeine and cigarettes for 24 h and to fast for 2 h before each study day.

On the study day (i.e. the day after they had completed each course of frusemide tablets), the subjects attended our department at 08.00 h. Each subject was given randomly, a different tablet on each visit day which comprised of either a placebo tablet, enalapril 20 mg or losartan 50 mg.

Subjects rested quietly in the supine position throughout the study period. An 18G intravenous cannula was inserted into a right forearm vein for drug infusions and blood sampling. After 45 min of bedrest, baseline values of blood pressure (BP) and heart rate (HR) were measured noninvasively in triplicate using a semiautomatic sphygmomanometer (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA) with the cuff being placed around the subjects left arm. A 12 lead electrocardiogram and venous blood (15ml) for baseline aldosterone and Ang II assays were also obtained.

The haemodynamic and baroreceptor assessments were carried out after 6 h following ingestion of the oral medication as the haemodynamic effects of both a single dose of oral losartan and enalapril are known to peak after 6 h [16, 17]. Further triplicate recordings of resting blood pressure, heart rate and continuous 12-lead ECGs were obtained before the reflex baroreceptor response to a vasopressor agent, phenylephrine (PE), was assessed. Intravenous PE was administered in stepwise 10 min infusions (0.2–3.6 $\mu g\,kg^{-1}\,min^{-1}$) by use of an infusion pump (IMED, San Diego, CA). The infusion was stopped when a 35–40 mmHg rise in systolic arterial pressure had been achieved. The average systolic BP, HR and R-R interval obtained from continuous ECG recordings between 8 and 10 min after each infusion dose were recorded. After completion of these measurements with PE, HR and BP were allowed to return to baseline values.

Baroreflex sensitivity (BRS) assessment

The R-R intervals were plotted against the systolic blood pressure in a graph, and a computerised curve fit was then carried out to establish a linear portion of the line of best fit. As in previous studies [8, 9, 18], only regression lines that had a correlation coefficient of >0.8 were used; the slope of the linear portion of this relationship ((RR/ΔsBP) was taken as an index of baroreflex sensitivity (BRS). The method of assessment of the baroreflex using an infusion of PE has been previously shown to be reproducible [18].

Aldosterone and angiotensin II assays

Venous blood samples (5 ml) in lithium heparin tubes and 10 ml venous samples in chilled glass tubes containing a solution of 0.05 $mol\,l^{-1}$ *o*-phenantroline, 2 $g\,l^{-1}$ neomycin, 0.125 $mol\,l^{-1}$ EDTA (disodium salt) and 2% ethanol, were collected for measurements of aldosterone and Ang II levels, respectively. The samples were centrifuged at 4° C and the plasma was separated and stored at $-20°$ C (aldosterone) and $-70°$ C (Ang II) until assayed. Commercially available radioimmunoassay kits (Sorin Biomedica, Saluggia, Italy, and Nichols Institute Diagnostics B.F., Nieuweweg, The Netherlands) were used for the aldosterone and Ang II assays, respectively.

Statistical analysis

All data were analysed using the Statgraphics software package (STSC Softwear Publishing Group, Rockville, MD, USA). Multiple analysis of variance, using subjects and treatment as within factors, and Bonferroni multiple range tests were performed to determine the significance of the effects of losartan and enalapril on the haemodynamic response to phenylephrine. The relationships between R-R intervals and systolic BP were studied by correlation and linear regression analyses; BRS between the placebo and treatment groups were analysed using the paired Student's *t*-test. Differences were considered statistically significant if $P<0.05$.

Results

Baseline measurements

Resting haemodynamic and biochemical measurements were similar at all study visits prior to administration of the study medications (Table 1). As expected, basal plasma Ang II and aldosterone levels were elevated as a result of frusemide-

Table 1 Baseline values. Results are expressed as means ± s.d. Statistical significance: ⋆$P<0.004$ compared with placebo.

		Placebo	*Enalapril*	*Losartan*
Heart rate (beats min^{-1})	Pre-dose	67.6 (4.6)	66.6 (9.1)	69.1 (9.4)
	6 h post-dose	68.0 (7.4)	67.1 (8.4)	68.8 (7.1)
Systolic BP (mmHg)	Pre-dose	117.6 (9.9)	117.1 (7.6)	118.5 (7.1)
	6 h post-dose	119.3 (8.5)	107.5 (9.8)⋆	110.1 (7.4)⋆
R-R interval (ms)	Pre-dose	892 (62)	916.5 (122)	883 (115)
	6 h post-dose	892 (96)	907 (108)	881 (89)
Plasma Ang II ($pg\ ml^{-1}$)	Pre-dose	42.6 (34.4)	40.7 (19.9)	44.9 (29.0)
Plasma aldosterone ($pg\ ml^{-1}$)	Pre-dose	194 (189)	113 (63)	141 (79)

induced salt depletion. At 6 h following ingestion of study medication, resting blood pressure was significantly reduced with both losartan and enalapril by 8.4 mmHg (95% CI 4.2, 12.6; $P=0.0038$) and 9.6 mmHg (95% CI 4.6, 14.6; $P=0.004$), respectively, compared with placebo. However, there were no significant differences with resting heart rate either at the start or at 6 h after medication.

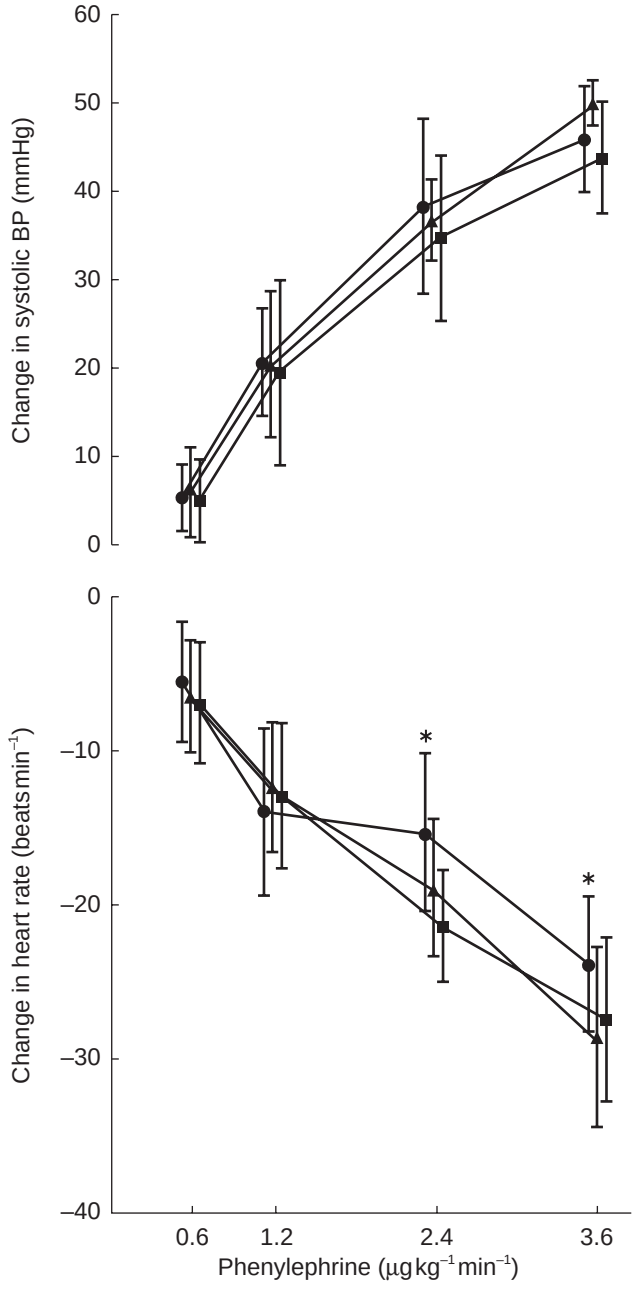

Figure 1 Change in heart rate (ΔHR) and blood pressure (ΔsBP) responses to incremental infusions of phenylephrine. Values are mean ± s.d. ● placebo, ▲ enalapril, ■ losartan ⋆$P<0.05$ compared with placebo.

Baroreceptor assessment (Figures 1,2, Table 2)

Systolic blood pressure and reflex heart rate increased and decreased, respectively, in a stepwise fashion in response to the phenylephrine infusion on all 3 study days. Whereas no significant differences in BP responses were observed with any of the study medications, reflex heart rate responses to phenylephrine were significantly increased with both enalapril and losartan compared to placebo ($P<0.05$). The (RR/(sBP ratio, taken as a measure of BRS was significantly increased with enalapril [$12.2+4.6$ ms $mmHg^{-1}$ (mean ± s.d.)] and losartan [$11.9+3.6$ ms $mmHg^{-1}$] compared with placebo [$9.2+4.5$ ms $mmHg^{-1}$]; i.e. enalapril and losartan increased the (RR/ΔsBP ratio by 3.0 ms $mmHg^{-1}$ (95%CI 0.5, 5.6; $P<0.05$) and 2.8 ms $mmHg^{-1}$ (95%CI 0.6, 5.0; $P<0.038$), respectively. There were however, no significant differences between losartan and enalapril [mean difference 0.25 (95%CI −1.6, 2.1)]. The individual BRS indices are displayed in Figure 2.

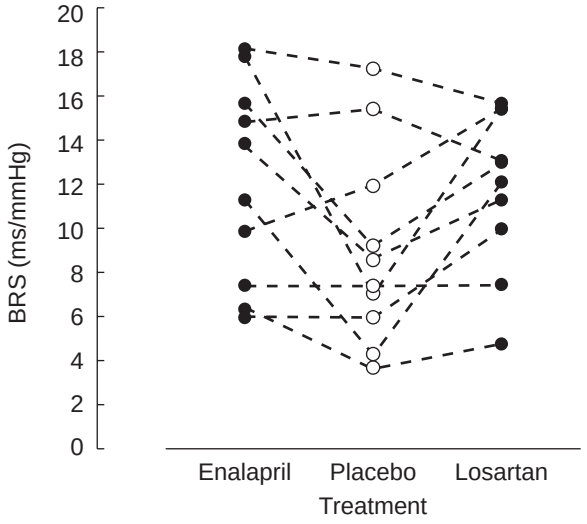

Figure 2 Individual baroreflex sensitivity (BRS) data. The individual BRS indices (slope of the linear regression line ΔRR/ΔsBP) in response to each of the three treatments are displayed.

Discussion

In this study, the haemodynamic effects of a single dose of oral losartan potassium and a single dose of oral enalapril maleate were examined in salt-depleted normotensive subjects pretreated with diuretics. Assessments were made 6 h after oral administration of the respective medications i.e. at the time when the haemodynamic effects of the drugs are maximal [16, 17]. The hypotensive effect of a single dose of 50 mg losartan was comparable with that of 20 mg enalapril (systolic BP reduced by 8.4 mmHg [95% CI 4.2, 12.6] and 9.6 mmHg [95% CI 4.6, 14.6], respectively). In accordance with data from other studies [16, 17, 19, 20] resting blood pressure was significantly reduced by both drugs but resting heart rate was unaffected.

The absence of reflex tachycardia accompanying blood pressure reduction has been attributed to the parasympathetic activity of these drugs. The influence of Ang II on the cardiac vagal activity is well established in both animal studies [21, 22] and human studies involving steady state infusions of Ang II [7]. Although in disease states such as CHF, ACE inhibitors have been shown to enhance baroreceptor function [8, 9], the evidence for such a role for endogenous Ang II in healthy man has been conflicting. In sodium replete hypertensive subjects, captopril has been shown to cause displacement of the baroreceptor set-point but no modification of the BRS during activation by phenylephine [23, 24]. However, hypertensive patients are known to have a blunted baroreflex function [24, 25] which might confuse the picture. Hence, only studies in normotensive subjects will allow a true assessment of the effect of Ang II blockade *per se* on baroreceptor function. Amongst normotensive subjects, Ibsen *et al.* [20] found that enalapril improved BRS function whereas Giulicelli *et al.* [26] did not. In the only human study involving AT1 receptor antagonists, losartan had no effect on baroreflex sensitivity, although this was measured by the gain of the transfer function relating BP to pulse interval rather than by more standard techniques [14]. One of the possible reasons for the contradictory data in the literature may be related to the differences in the salt status and degree of endogenous Ang II activation in the different study populations. The latter two studies above [14, 26] were carried out in normotensives with normal salt status whereas in the study by Ibsen *et al.* [20], the subjects were mildly sodium depleted. This observation may be important suggesting that the influence of endogenous Ang II on the autonomic and vascular tone may only become prominent during an activated RAAS state e.g. during salt depletion. It has been shown in a recent animal model that Ang II blockade improved the baroreflex response to a greater extent in rats fed with a sodium deficient diet compared with those on a high sodium diet [27]. The effects of raised endogenous Ang II is clinically relevant in a cardiovascular diseases such as CHF and hypertension where the RAAS is activated and may even be further exacerbated by diuretic therapy. Recent data even suggest that the RAAS is activated in hypercholesterolaemic patients [28] which may make our findings relevant to many disease groups.

The effects of raised endogenous Ang II on reflex baroreceptor function were assessed in this study. The subjects in the study were pretreated with frusemide to activate the RAAS. The reflex bradycardic response to phenylephrine was significantly increased following treatment with enalapril and losartan. In addition, the slopes of the (RR/ΔsBP linear regression line were also significantly increased. These observations support our hypothesis that raised endogenous Ang II levels do contribute to baroreceptor dysfunction and that Ang II blockade, either by ACE inhibition or direct antagonism at the receptor level, would reverse it. These findings are also in agreement with observations from animal models where both losartan [27, 29] and enalapril [29] have been shown to enhance baroreceptor sensitivity.

It is also interesting to note in this study that the effects of losartan were comparable with those of enalapril. Although minor differences between the two clearly could not be excluded, we were able to exclude large or significant differences. Direct Ang II receptor antagonists such as losartan lack the bradykinin potentiation seen with ACE inhibition. Although there are beneficial effects associated with bradykinins, the lack of bradykinin-related adverse

Table 2 Changes in haemodynamic parameters in response to phenylephrine infusion. Values are mean ± s.d. Statistical significance: ⋆$P<0.01$; †$P<0.05$ compared with placebo.

Dose PE ($\mu g\ kg^{-1}\ min^{-1}$)	*Placebo*	*Enalapril*	*Losartan*
		ΔsBP (mmHg)	
0.6	5.3 ± 3.8	5.9 ± 5.1	5.0 ± 4.6
1.2	20.6 ± 6.1	20.4 ± 8.3	19.5 ± 10.4
2.4	38.1 ± 9.8	36.6 ± 4.5	34.6 ± 9.3
3.6	45.6 ± 6.0	49.6 ± 2.6	43.6 ± 6.4
		ΔHR (beats min^{-1}*)*	
0.6	5.6 ± 3.9	6.6 ± 3.6	7.0 ± 3.9
1.2	14.0 ± 5.4	12.5 ± 4.2	13.0 ± 4.7
2.4	15.4 ± 5.1	19.0 ± 4.4⋆	21.4 ± 3.6⋆
3.6	23.9 ± 4.4	28.6 ± 5.8†	27.5 ± 5.3⋆
		ΔR-R interval (ms)	
0.6	86 ± 64.5	101.5 ± 68	110 ± 79
1.2	250 ± 127	222 ± 113	224 ± 127
2.4	280 ± 125	376 ± 142⋆	421 ± 149⋆
3.6	517 ± 204	738 ± 309⋆	644 ± 269

effects makes AT1 receptor antagonists an attractive alternative to ACE inhibitors. The recent ELITE trial [15] suggest that losartan may be even better than ACE inhibitors in terms of reducing mortality and in particular sudden deaths in heart failure. Although baroreflex dysfunction is thought to be a key process leading to ventricular dysrhythmias and sudden deaths, our study did not show any large differences in baroreceptor modulation between the two strategies. There may be several explanations for this. Firstly, the mechanisms for sudden death are multifactorial. Secondly, the number of deaths in the ELITE trial was small as it was not designed primarily as a mortality trial and the results may therefore occur by chance. Thirdly, there are inevitably, some limitations to our study.

Infusions rather than boluses of pressor stimuli were used in this study, allowing for baroreceptor 'resetting' to occur and hence reducing or dampening any change in baroreceptor response. This may mean that potentially small differences in baroreceptor response between the two treatments for instance, may have gone undetected. BRS measurements by infusion method may not be equivalent to the bolus method, but the infusion method has been shown to be reproducible [18].

Infusions were used in this study firstly, as it allowed us to monitor HR and BP changes at steady state noninvasively at each incremental dose, and hence avoiding the need for invasive beat-to-beat intra-arterial measurements as required by the bolus method. Secondly, noninvasive beat-to-beat analysis using the FINAPRES is now difficult in the United Kingdom as the FINAPRES machines are no longer available. Therefore, although our measurements may not exactly match the beat-to-beat method, our technique has the advantage that our readings were taken at steady state and more importantly still each of our readings were taken in triplicate, which should minimize random measurement error. Furthermore we were more interested in *changes or differences* in baroreceptor sensitivities between two treatments rather than in using absolute levels of BRS to compare one population with another.

Despite these limitations, our data clearly indicate that blocking endogenous Ang II in man improves baroreceptor function. Both strategies, AT1 receptor antagonism and ACE inhibition appear to be equally effective in restoring baroreceptor function in salt-depleted normotensive subjects. This may be clinically relevant in conditions such as CHF; the long-term effects of these treatments are currently being evaluated in the ongoing mortality trial, ELITE II.

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